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CYTOKINES IN ACUTE AND CHRONIC INFLAMMATION

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1. ABSTRACT

Inflammation is mediated by a variety of soluble factors, including a group of secreted polypeptides known as cytokines. Inflammatory cytokines can be divided into two groups: those involved in acute inflammation and those responsible for chronic inflammation. This review describes the role played in acute inflammation by IL-1, TNF-α, IL-6, IL-11, IL-8 and other chemokines, G-CSF, and GM-CSF. It also describes the involvement of cytokines in chronic inflammation. This latter group can be subdivided into cytokines mediating humoral responses such as IL-4, IL-5, IL-6, IL-7, and IL-13, and those mediating cellular responses such as IL-1, IL-2, IL-3, IL-4, IL-7, IL-9, IL-10, IL-12, interferons, transforming growth factor-β, and tumor necrosis factor α and β. Some cytokines, such as IL-1, significantly contribute to both acute and chronic inflammation. This review also summarizes features of the cell-surface receptors that mediate the inflammatory effects of the described cytokines.

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2. INTRODUCTION

Inflammation, the response of tissue to injury, is characterized in the acute phase by increased blood flow and vascular permeability along with the accumulation of fluid, leukocytes, and inflammatory mediators such as cytokines. In the subacute/chronic phase (hereafter referred to as the chronic phase), it is characterized by the development of specific humoral and cellular immune responses to the pathogen(s) present at the site of tissue injury. During both acute and chronic inflammatory processes, a variety of soluble factors are involved in leukocyte recruitment through increased expression of cellular adhesion molecules and chemoattraction. Many of these soluble mediators regulate the activation of the resident cells (such as fibroblasts, endothelial cells, tissue macrophages, and mast cells) and the newly recruited inflammatory cells (such as monocytes, lymphocytes, neutrophils, and eosinophils), and some of these mediators result in the systemic responses to the inflammatory process (*e.g.* fever, hypotension, synthesis of acute phase proteins, leukocytosis, cachexia). The soluble factors that mediate these responses (reviewed in ref. 1) fall into four main categories: (1) inflammatory lipid metabolites such as platelet activating factor (PAF) and the numerous derivatives of arachidonic acid (prostaglandins, leukotrienes, lipoxins), which are generated from cellular phospholipids; (2) three cascades of soluble proteases/substrates (clotting, complement, and kinins), which generate numerous pro-inflammatory peptides; (3) nitric oxide, a potent endogenous vasodilator, whose role in the inflammatory process has only recently begun to be explored; and (4) a group of cell-derived polypeptides, known as cytokines, which to a large extent orchestrate the inflammatory response, *i.e.* they are major determinants of the make-up of the cellular infiltrate, the state of cellular activation, and the systemic responses to inflammation. Most cytokines are multifunctional. They are pleiotropic molecules that elicit their effects locally or systemically in an autocrine or paracrine manner. Cytokines are involved in extensive networks that involve synergistic as well as antagonistic interactions and exhibit both negative and positive regulatory effects on various target cells.

This review will focus on inflammatory cytokines, including a description of their primary activities related to acute and chronic inflammation, and a discussion of their cell surface receptors.

3. DISCUSSION

3.1 Cytokines involved in acute inflammation:

Several cytokines play key roles in mediating acute inflammatory reactions, namely IL-1, TNF-α, IL-6, IL-11, IL-8 and other chemokines, G-CSF, and GM-CSF (Figure 1). Of these, IL-1 (α and β) and TNF are extremely potent inflammatory molecules: they are the primary cytokines that mediate acute inflammation induced in animals by intradermal injection of bacterial lipopolysaccharide and two of the primary mediators of septic shock.

3.1.1 Interleukin-1:

The cDNAs for IL-1α and β were cloned in 1984. They are encoded by two different genes, both located on human chromosome 2. Their size ranges from 22-31 kDa for cell-associated molecules, and 17.5 kDa for the secreted molecule (2). Their main cellular sources are mononuclear phagocytes, fibroblasts, keratinocytes, and T and B lymphocytes. Previous synonyms--endogenous pyrogen (EP), mononuclear cell factor, and lymphocyte-activating factor (LAF)--emphasize the role of IL-1 in inflammation. Both IL-1α and IL-1β can trigger fever by enhancing prostaglandin E_2 (PGE_2) synthesis by the vascular endothelium of the hypothalamus (2) and can stimulate T cell proliferation. In addition, IL-1 elicits the release of histamine from mast cells at the site of inflammation (Figure 2). Histamine then triggers early vasodilation and increase of vascular permeability. The pro-inflammatory effects of IL-1 can be inhibited by IL-1 receptor antagonist (IL-1Ra), originally referred to as IL-1 inhibitor. IL-1Ra is produced by immune complex- or IL-4-stimulated macrophages and by TNF- or GM-CSF-stimulated neutrophils. It bears approximately 20-25% homology at the amino acid level to IL-1α and IL-1β. IL-1Ra inhibits IL-1 action by competing with IL-1 for binding to the IL-1 receptor (IL-1R) (3,4).

3.1.2 Tumor necrosis factor:

Tumor necrosis factors-(TNF)α and β are cytokines that bind to common receptors on the surface of target cells and exhibit several common biological activities. Human TNF-α and TNF-β are of 17 and 25 kDa, respectively. Their corresponding cDNAs were cloned in 1984, and the genes encoding the factors have been mapped to chromosome 6 in humans (5), within the region of the major histocompatibility complex (MHC). TNF-α, or cachectin, exists as a trimer (6) and is one of the products of activated macrophages/monocytes, fibroblasts, mast cells, and some T and natural killer (NK) cells (7,8) (Figure 2). TNF-α and IL-1 share several pro-inflammatory properties. Like IL-1, TNF-α can induce fever, either directly via stimulation of PGE_2 synthesis by the vascular endothelium of the hypothalamus, or indirectly by inducing release of IL-1 (2). Both cytokines can stimulate the production of collagenase and PGE_2 by synovial cells and thus are believed to contribute to joint damage in inflammatory conditions such as rheumatoid arthritis (2). TNF-α also shares an important inflammatory property with IL-6 and IL-11, *i.e.* the induction of acute phase reactant protein production by the liver. TNF-α and IL-1 further exert secondary inflammatory effects by stimulating IL-6 synthesis in several cell types. IL-6 then mediates its

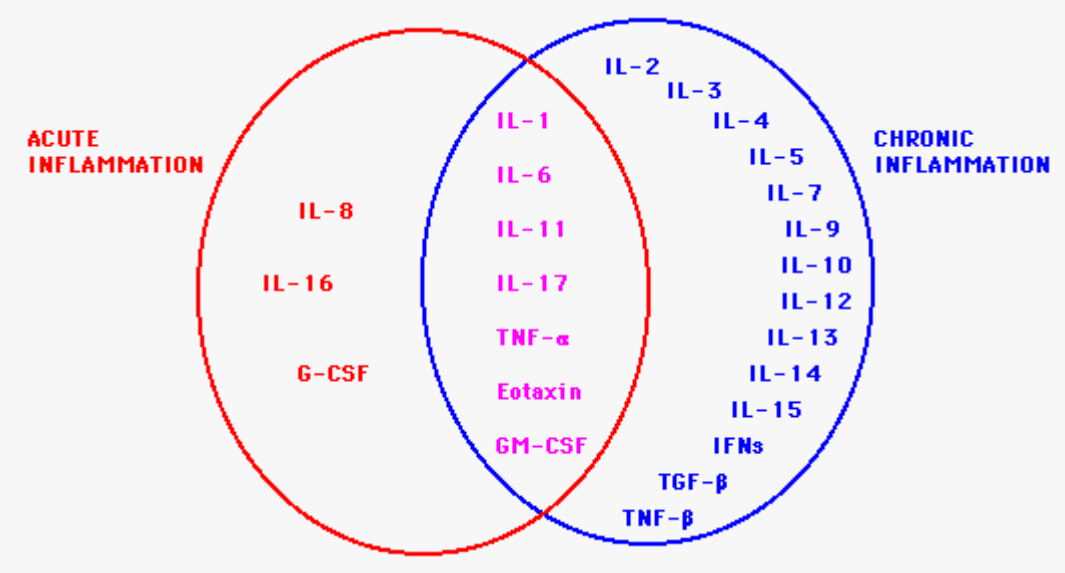

FIGURE 1: Cytokines involved in acute and chronic inflammatory responses.

own effects and those of TNF-α and IL-1 in inducing fever and the acute phase response (2), thereby perpetuating the inflammatory response through a cascade of cytokines with overlapping properties.

TNF-β, also known as lymphotoxin, is produced by activated T and B lymphocytes. It binds to the same high affinity receptors as TNF-α. Its properties are similar to those of TNF-α and include the induction of apoptosis (programmed cell death) in many types of transformed, virally infected, and tumor cells, and the stimulation of several PMN effector functions (9).

Although in general the effects of cytokines are exerted locally at the site of their production (autocrine and paracrine), TNF-α and TNF-β, as well as IL-1 and IL-6, have major systemic (endocrine) effects when either produced acutely in large amounts, as in the case of bacterial sepsis, or chronically in lesser amounts, as in the case of chronic infections. During sepsis with Gram negative organisms, lipopolysaccharides (endotoxin) released from bacteria trigger the widespread production of TNF-α (and subsequently IL-1 and IL-6) by macrophages. The systemic release of these cytokines has been shown to be responsible for the fever and hypotension that characterize septic shock (8). In an analogous fashion, the production of large amounts of TNF-β by T lymphocytes in response to "superantigens" such as staphylococcal toxic shock syndrome toxin and enterotoxins are responsible for many of the systemic manifestations (fever, hypotension) of infections with toxin-producing Gram positive organisms (10,11). In addition, the chronic production of TNF is believed to be responsible for the metabolic alterations which result in the cachexia associated with chronic parasitic infections and some cancers (8).

3.1.3 Interleukin-6:

Previous synonyms of IL-6 illustrate some of its biologic activities. They include interferon-β_2 (IFN-β_2), hybridoma/plasmacytoma growth factor, hepatocyte-stimulating factor, B cell stimulatory factor 2 (BSF-2), and B cell differentiation factor (BCDF). IL-6 is a glycoprotein ranging from 21 to 28 kDa depending on the degree of post-translational modification. The IL-6 cDNA was cloned in 1986 and the gene encoding IL-6 was mapped to chromosome 7 in humans (12). IL-6 is produced by a variety of cells including mononuclear phagocytes, T cells, and fibroblasts (12-14). In addition to the stimulation of acute phase protein synthesis by the liver, IL-6 acts as a growth factor for mature B cells and induces their final maturation into antibody-producing plasma cells. It is involved in T cell activation and differentiation, and participates in the induction of IL-2 and IL-2 receptor expression (Figure 2). Some of the regulatory effects of IL-6 involve inhibition of TNF production, providing negative feedback for limiting the acute inflammatory response. Upregulation of IL-6 production has been observed in a variety of chronic inflammatory and autoimmune disorders such as thyroiditis, type I diabetes, rheumatoid arthritis (15,16), systemic sclerosis (17), mesangial proliferative glomerulonephritis and psoriasis, and neoplasms such as cardiac myxoma, renal cell carcinoma, multiple myeloma, lymphoma, and leukemia (15).

3.1.4 Interleukin-11:

IL-11 is a cytokine of 24 kDa encoded by a gene located on the long arm of chromosome 19. The corresponding cDNA was cloned in 1990 (18). IL-11

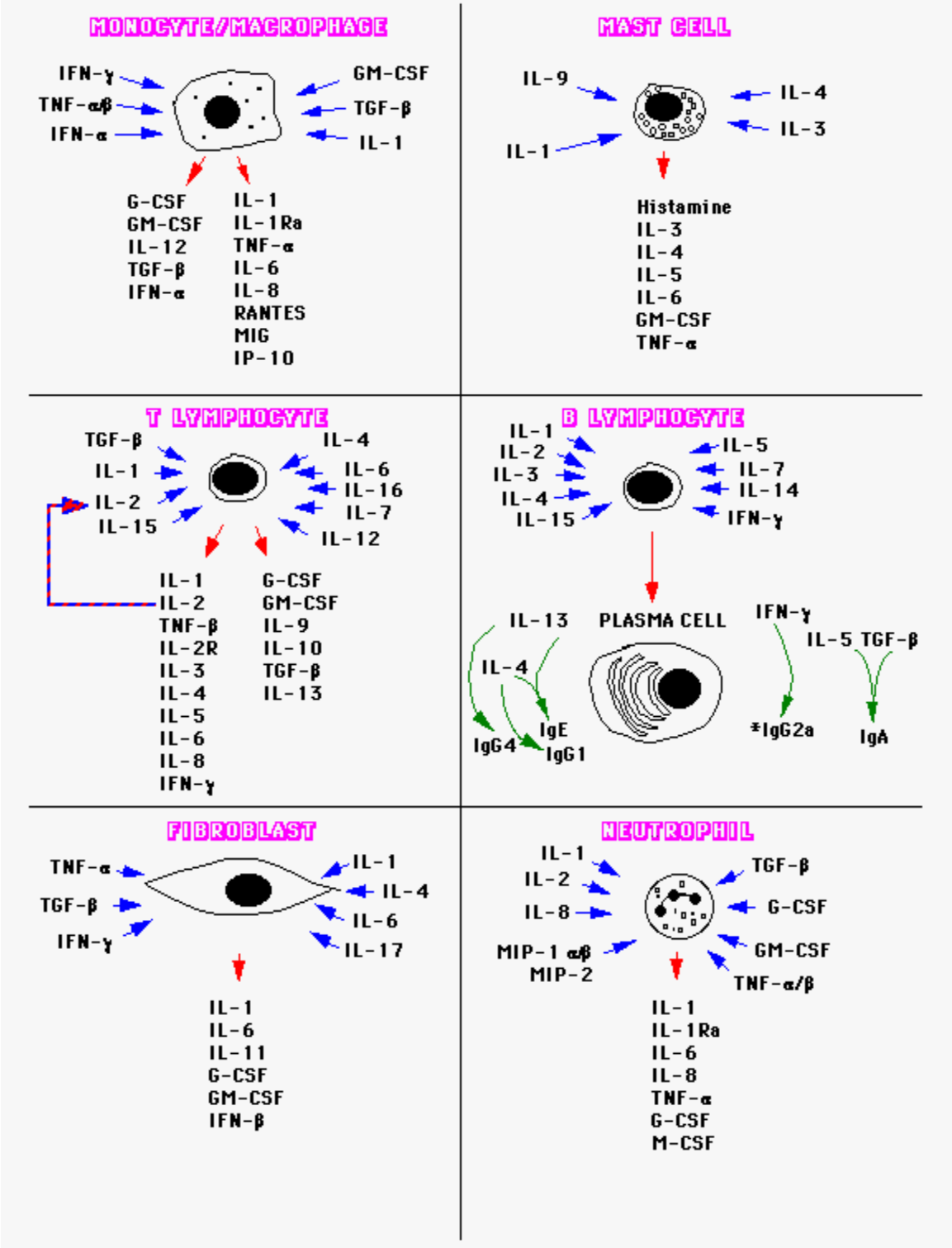

FIGURE 2: Inflammatory cytokines, their primary sources and target cells. *IFN-γ stimulates IgG2α production in the mouse.

is produced by bone marrow stromal cells and by some fibroblasts. It is a functional homologue of IL-6 and can replace IL-6 for the proliferation of certain plasmacytoma cell lines (18) and in the induction of acute phase protein secretion in the liver (19).

Additional IL-11 activities include stimulation of T cell-dependent B cell immunoglobulin secretion, increased platelet production, and induction of IL-6 expression by $CD4^+$ T cells.

3.1.5 Interleukin-8/chemokines:

IL-8 and other low molecular weight chemokines (*e.g.* platelet factor 4, IP-10, mig, ENA-78, macrophage inflammatory protein (MIP)-1α and β, MIP-2, monocyte chemoattractant protein-1 (MCP-1/JE), RANTES) belong to a chemotactic cytokine family and are responsible for the chemotactic migration and activation of neutrophils and other cell types (such as monocytes, lymphocytes, basophils, and eosinophils) at sites of inflammation (20,21). The two subsets of the chemokine family, "CXC" (or α), "C-C" (or β) are divided based on presence or absence of an amino acid between the first two of four conserved cysteines. A recent third subset, "C", has only two cysteines and to date only one member, IL-16, has been identified (22). Chemokines have been implicated in inflammatory conditions from acute neutrophil-mediated conditions such as acute respiratory distress syndrome to allergic asthma, arthritis, psoriasis, and chronic inflammatory disorders. To date, at least 27 chemokines have been described. The product of many cell types, including mononuclear phagocytes, antigen-activated T cells, endothelial and epithelial cells, and even neutrophils, IL-8 was previously known as neutrophil chemotactic factor (NCF) and neutrophil activating protein (NAP-1) (20,23). It is the most thoroughly studied chemokine and therefore serves as a prototype for discussing the biologic properties of this rapidly growing family of inflammatory mediators. It consists of a 6-8 kDa protein whose cDNA was cloned by three different laboratories between 1987 and 1989. The corresponding gene has been mapped to chromosome 4 in humans (24). Its main inflammatory impact lies in its chemotactic effects on neutrophils and its ability to stimulate granulocyte activity. In addition, IL-8, IL-1, and TNF are involved in neutrophil recruitment by upregulating cell-surface adhesion molecule expression (such as endothelial leukocyte adhesion molecule, ELAM-1, and intracellular adhesion molecule, ICAM-1), thereby enhancing neutrophil adherence to endothelial cells (2) and facilitating their diapedesis through vessel walls. Thus, IL-8 mediates the recruitment and activation of neutrophils in inflamed tissue (25). IL-8 can be detected in synovial fluid from patients with various inflammatory rheumatic diseases (26), and mucosal levels of IL-8 are elevated in patients with active ulcerative colitis (27).

Other members of this cytokine family, such as NAP-2, GROα, GROβ, GROγ, ENA-78, RANTES, MCP-1, MCP-2, MCP-3, platelet factor 4, MIP-1α/β, and MIP-2, are also likely to play important roles in acute inflammation via their shared effects on cell migration. MCP-1 is a chemokine identified in supernatants of blood mononuclear cells. Its production in monocytes is enhanced by inflammatory cytokines. MIP-1α and MIP-1β induce monocyte and T lymphocyte migration. MIP-1α, MCP-1, and MIP-2 have been implicated in the pathogenesis of rheumatoid arthritis where they are believed to recruit mononuclear cells into the inflamed regions of the synovium (28). Several other members of the IL-8/chemokine family have been identified but their biologic effects are as yet poorly defined. Two recently identified chemokines, eotaxin and IL-16, have some unique properties and are described below.

3.1.6 Eotaxin:

Eotaxin was initially described in rodent models of asthma. The human homolog has since been cloned and consists of a 74-amino acid protein. Eotaxin has two of four adjacent cysteines which are highly conserved among β (C-C) chemokines. At the amino acid level, it is most homologous to the MCP proteins. Eotaxin is a specific chemoattractant for eosinophils. It is produced by cytokine-stimulated epithelial and endothelial cells as well as IL-3-stimulated eosinophils. Eotaxin is implicated in inflammatory bowel disease where its mRNA levels are markedly elevated, especially in ulcerative colitis (29)

3.1.7 Interleukin-16:

IL-16 was originally identified as a chemotactic factor known as lymphocyte chemoattractant factor or lymphotactin. It is the only member of the "C" family of chemokines. The gene encoding IL-16 has been mapped to human chromosome 1 (22). IL-16 is an unusual cytokine in that preformed IL-16 is stored in $CD8^+$ lymphocytes and is secreted upon stimulation with histamine or serotonin (30). It induces chemotaxis of $CD4^+$ T lymphocytes (31,32) (Figure 2) and is believed to initiate T-cell mediated inflammation in asthma (33).

3.1.8 Interleukin-17:

The human IL-17 cDNA was cloned in 1995 based on homology with murine CTLA8 (34). A 1.9 Kb cDNA was found to encode a protein of 17.5 kDa homologous to a product of Herpesvirus saimiri (HVS13) (34). IL-17 is a product of activated T lymphocytes and its biologic activities include stimulation of IL-6 and IL-8 production and enhanced ICAM-1 expression on human foreskin fibroblasts (34).

3.1.9 Colony stimulating factors:

Colony stimulating factors (CSF) are named according to the target cell type whose colony formation in soft agar cultures of bone marrow they induce (35). Of the CSF's, granulocyte-CSF (G-CSF) and granulocyte macrophage-CSF (GM-CSF) participate in acute inflammation. G-CSF was cloned in 1986 and its gene was mapped to chromosome 17 (36). It is a non-glycosylated protein of 19 kDa molecular weight. GM-CSF is a 22 kDa protein. Its full length cDNA sequence was obtained in 1985 and its gene was mapped to chromosome 5 in humans (36). Monocytes, T cells, fibroblasts and endothelial cells activated by macrophage products such as IL-1 or TNF, can produce G-CSF and GM-CSF. Both

CSF's can stimulate neutrophils, while GM-CSF can also activate effector functions of eosinophils and mononuclear phagocytes (Figure 2). An example of the pathophysiologic role of GM-CSF is the airway inflammation accompanying asthma, where the implicated cytokines include IL-3, IL-5, and GM-CSF which perpetuate eosinophil activation and survival. In this scenario, the source of GM-CSF may be the alveolar macrophages which are reported to produce two to threefold higher levels of GM-CSF than control macrophages (37). Another possible source for all three cytokines are T cells present in the airways. Additional cytokines such IL-4, IL-13 (both stimulatory) and IFN-γ (inhibitory) may be involved in the control of IgE synthesis, while IL-1 and TNF-α may contribute to the airway inflammation by upregulation of endothelial adhesion molecule expression (37).

4. CYTOKINES INVOLVED IN CHRONIC INFLAMMATION:

Chronic inflammation may develop following acute inflammation and may last for weeks or months, and in some instances for years. During this phase of inflammation, cytokine interactions result in monocyte chemotaxis to the site of inflammation where macrophage activating factors (MAF), such as IFN-γ, MCP-1, and other molecules then activate the macrophages while migration inhibition factors (MIF), such as GM-CSF (38) and IFN-γ, retain them at the inflammatory site. The macrophages contribute to the inflammatory process by chronically elaborating low levels of IL-1 and TNF which are responsible for some of the resulting clinical symptoms such as anorexia, cachexia, fever, sleepiness, and leukocytosis.

The cytokines known to mediate chronic inflammatory processes can be divided into those participating in humoral inflammation, such as IL-3, IL-4, IL-5, IL-6, IL-7, IL-9, IL-10, IL-13, and transforming growth factor-β (TGF-β), and those contributing to cellular inflammation such as IL-1, IL-2, IL-3, IL-4, IL-7, IL-9, IL-10, IL-12, interferons (IFNs), IFN-γ inducing factor (IGIF), TGF-β, and TNF-α and -β (Figure 1).

4.1.1 Cytokines primarily involved in the humoral inflammatory response:

4.1.1.1 Interleukin-3:

IL-3, also called multi-CSF, is produced by activated T cells and mast cells. The molecular weight of IL-3 ranges from 14 to 36 kDa. The cloning of the corresponding cDNA was reported in 1984, and the IL-3 gene has been localized to chromosome 5 (39). It stimulates eosinophils and B cell differentiation while it inhibits lymphokine-activated killer (LAK) cell activity (40) (Figure 2). IL-3 shares several biological activities with GM-CSF (41).

4.1.1.2 Interleukin-4:

IL-4 is expressed as a 15-19 kDa protein and exists as a dimer. The IL-4 gene has been mapped to human chromosome 5, and the corresponding cDNA was cloned in 1986 (42,43). IL-4 is produced by $CD4^+$ (T_H) cells, mast cells, and basophils. It induces $CD4^+$ T cells to differentiate into T_H2 cells while suppressing the development of T_H1 cells. It also acts as a B cell, T cell, and mast cell growth factor, it enhances class II MHC expression on B cells, and it promotes immunoglobulin class switching to IgG_1 and IgE (42,43) (Figure 2). In fact, IL-4 is necessary for IgE response induction, and its absence also leads to significantly lower levels of IgG_1 in T cell-dependent immune responses (44). The stimulatory effects of IL-4 on IgG_1 and IgE production and on MHC class II induction are downregulated by IFN-γ, a cytokine whose functions are antagonized by IL-4 and vice versa. IL-4 also stimulates collagen (45) and IL-6 production (46) by human dermal fibroblasts, and may thus play a role in the pathogenesis of fibrotic diseases such as systemic sclerosis. In rheumatoid arthritis, on the other hand, IL-4 appears to exhibit some anti-inflammatory properties by inhibiting the production of several pro-inflammatory cytokines such as IL-1, IL-6, IL-8, and TNF-α, by synovial membranes of rheumatoid arthritis patients (47).

4.1.1.3 Interleukin-5:

Cloned in 1987, the IL-5 cDNA encodes a protein of 20-22 kDa which has an apparent molecular weight of 45 kDa upon dimerization. Like IL-4, the gene for IL-5 has also been mapped to chromosome 5 in humans (43). IL-5, also known as B cell growth factor II (BCGFII) and T cell replacing factor (TRF), is produced by $CD4^+$ T helper cells as well as NK cells, and exists as a dimer linked by disulfide bonds (40). IL-5 is involved in eosinophil differentiation and activation and stimulation of immunoglobulin class switching to IgA. Other properties of IL-5 include increased activation of B cell proliferation, and enhancement of T cell cytotoxicity (43). The combined production of IL-4 and IL-5 by $CD4^+$ T_H2 cells therefore results in IgE and IgA production and mast cell and eosinophil stimulation.

4.1.1.4 Interleukin-7:

IL-7 is a cytokine of about 25 kDa whose cDNA was cloned in 1989. Its gene has been mapped to human chromosome 8 (48). IL-7, a cytokine purified as a pre-B cell growth factor, is a bone marrow and thymic stromal cell product. It stimulates the development of pre-B and pre-T cells and acts as a growth factor for B cells, T cells, and early thymocytes (48) (Figure 2).

4.1.1.5 Interleukin-9:

IL-9 is another cytokine produced by $CD4^+$ T helper (T_H2) cells as well as some B lymphomas.

First described in the mouse, IL-9 was known as mast cell growth-enhancing activity (MEA) and murine T-cell growth factor P40 (49). The IL-9 cDNA was cloned in 1989 (50) and the gene encoding it was mapped to human chromosome 5 (51). Its production is IL-4 and IL-10, and thus IL-2-dependent. IL-9 is regulatory in nature in that it inhibits lymphokine production by IFN-γ-producing $CD4^+$ T cells and enhances the growth of $CD8^+$ T cells (52). In addition, IL-9 promotes the production of immunoglobulins by B cells and the proliferation of mast cells (53).

4.1.1.6 Interleukin-10:

IL-10 is also referred to as B cell-derived T cell growth factor and cytokine synthesis inhibitory factor (CSIF) because it inhibits IFN-γ production by activated T cells. The cDNA for human IL-10 was cloned in 1990 and found to encode an 18 kDa protein. IL-10 is produced by a variety of cell types, including $CD4^+$ T cells, activated $CD8^+$ T cells, and activated B cells (54). Its effects include reduction of antigen-specific T cell proliferation, inhibition of IL-2-induced IFN-γ production by NK cells, and inhibition of IL-4 and IFN-γ induced MHC class II expression on monocytes (55). Since IL-10 can be produced by T_H2 cells and inhibits T_H1 function by preventing T_H1 cytokine production (such as IFN-γ), IL-10 is considered a T cell cross-regulatory factor and has thus been referred to as an "anticytokine" (56). IL-10 also acts as a co-differentiation factor for cytotoxic T cells and a co-factor for T cell growth. Human IL-10 (hIL-10) shares 84% identity at the amino acid level with a homolog, viral IL-10 (vIL-10), which is encoded by the Epstein-Barr virus (57). vIL-10 shares with hIL-10 inhibitory effects on cytokine production and stimulatory effects on B cell growth (58).

4.1.1.7 Interleukin-13:

IL-13 was originally identified as a protein produced by activated murine T_H2 lymphocytes and referred to as P600 (59). The cDNA for IL-13 was recently cloned and the gene was mapped to human chromosome 5, closely linked to the gene encoding IL-4 (60). A 12-17 kDa protein, IL-13 exhibits anti-inflammatory activities by inhibiting the production of inflammatory cytokines, such as IL-1β, TNF-α, IL-8, and IL-6, by human peripheral blood monocytes induced with lipopolysaccharide (60). Inhibition of inflammatory cytokine production is also a characteristic of two other cytokines produced by T_H2 lymphocytes, namely IL-4 and IL-10. In addition, IL-13 enhances monocyte and B lymphocyte differentiation and proliferation, increases CD23 expression, and induces IgG_4 and IgE class switching (61).

4.1.1.8 Interleukin-14:

A product of malignant B and T cells as well as normal T cells, IL-14 is a 53 kDa B-cell growth factor (BCGF). Like IL-4, IL-14 has been shown to induce B cell proliferation. However, IL-14 inhibits immunoglobulin secretion (53). It has been suggested to play an important role in the aggressive form of B-cell type non-Hodgkin's lymphoma (62).

4.1.1.9 Transforming growth factor-β:

The transforming growth factor-β (TGF-β) family of cytokines includes three isoforms, TGF-β1, β2, and β3 which are encoded by separate genes yet bind to the same high affinity receptor. TGF-β functions as a 25 kDa homodimer consisting of two 12-kDa polypeptides (63). The human cDNA for TGF-β 1 was cloned in 1985 (64). It is produced by T cells, platelets, and monocytes. TGF-β inhibits T cell and NK cell proliferation and activation (Figure 2) and may play an important role in inflammation (64). At a site of injury, TGF-β stored in platelets is released upon degranulation. TGF-β then attracts monocytes and other leukocytes to the site, thus participating in the initial step of chronic inflammation. TGF-β then positively regulates its own production and the production and deposition of extracellular matrix components as well as the expression of integrins resulting in enhanced cell adhesion. It also inhibits collagenase production, and if expression is prolonged, it may result in progressive fibrosis analogous to unregulated tissue repair. Conditions in which a role for TGF-β has been suggested include mesangial proliferative glomerulonephritis and diabetic nephropathy in rats, pulmonary fibrosis, and systemic sclerosis (63). Another example of the role played by TGF-β in inflammation is collagen-induced arthritis in rats. In this model, TNF-α and TGF-β, when injected into the rat ankle joint, accelerate disease onset (65).

4.1.2 Cytokines involved primarily in the cellular inflammatory response:

4.1.2.1 Interleukin-2:

The human IL-2 cDNA was cloned in 1983 and the corresponding gene has been mapped to the long arm of chromosome 4 (66). IL-2 is a 15 kDa glycoprotein originally known as T cell growth factor (TCGF). It is secreted mainly by activated T helper cells. It acts as a growth factor/activator for T cells, NK cells, and B cells and promotes the development of lymphokine-activated killer (LAK) cells (40,53) (Figure 2). It therefore plays a critical role in regulating both cellular and humoral chronic inflammatory responses. Binding of IL-2 to the IL-2 receptor on T lymphocytes leads to cell proliferation, increased lymphokine secretion (IFN-γ, lymphotoxin, IL-4, IL-3, IL-5, GM-CSF), and enhanced expression of class II MHC molecules.

4.1.2.2 Interleukin-12:

IL-12, previously known as natural killer cell stimulatory factor (NKSF) and cytotoxic lymphocyte maturation factor (CLMF), was originally isolated from Epstein-Barr virus transformed B cells. It is a heterodimer composed of two subunits of 35

and 40 kDa. The cDNAs for both subunits were cloned in 1991 (67). Its biological activities include enhancement of cytotoxic T cells and lymphokine-activated killer (LAK) cell generation and activation, increased natural killer (NK) cell cytotoxicity, induction of activated T cell and NK cell proliferation, induction of IFN-γ production by NK cells and T cells, and inhibition of IgE synthesis by IL-4-stimulated lymphocytes via IFN-γ-dependent and independent mechanisms (67-69) (Figure 2). IL-12 is secreted by activated B cells, macrophages, and other antigen-presenting cells (APCs), but its production is inhibited by IL-4 and IL-10. In addition, the stimulatory effect of IL-12 on T_H1 development is antagonized by IL-4, a cytokine which promotes T_H2 cell development. Therefore, IL-12 plays an important role in cell-mediated inflammation and also contributes to the regulation of immunoglobulin production.

4.1.2.3 Interleukin-15:

IL-15 is a cytokine of approximately 15 kDa originally discovered as a T cell stimulatory activity (70) produced by activated monocytes, epithelial cells, and fibroblasts. IL-15 shares many biologic properties with IL-2 and mediates its activity via a multi-subunit high affinity receptor comprised of a unique alpha chain and the beta and gamma chains of the IL-2R. The human IL-15 gene has been mapped to chromosome 4 (70), similarly to IL-2. However, IL-15 does not exhibit any sequence homology with IL-2. IL-15 is produced by a large variety of cells including T lymphocytes and monocytes. It stimulates T lymphocyte and NK cell proliferation, as well as CTL and LAK activity (53). It enhances B cell expansion and immunoglobulin production (71) (Figure 2). It is also a T lymphocyte chemoattractant. IL-15 may be responsible for the recruitment and activation of T lymphocytes in the synovium of patients with rheumatoid arthritis where its levels have been found to be elevated (72).

4.1.2.4 Interferons:

The interferons are a group of cytokines originally identified by and named for their anti-viral activity (73). Their corresponding cDNAs were cloned in 1980-81. Type I interferons include IFN-α, an 18-20 kDa product of leukocytes, and IFN-β, a product of fibroblasts. They exhibit anti-viral as well as anti-proliferative properties and upregulate MHC class I expression. IFN-α is encoded by several genes clustered in the short arm of chromosome 9. However, only one gene, also localized to chromosome 9, codes for IFN-β . Type II interferon, immune interferon or IFN-γ, is a homodimer produced by activated T cells and NK cells. A single gene located on chromosome 12 encodes human IFN-γ which has a molecular weight of 20 or 25 kDa (monomer) depending on the extent of glycosylation (74). IFN-γ is known to enhance MHC class I and II expression on nucleated cells and to stimulate many of the effector functions of mononuclear phagocytes. While IFN-α and -β bind to a common receptor, IFN-γ recognizes a distinct and specific cell surface receptor. IFN-γ has been implicated in the pathogenesis of a variety of autoimmune and chronic inflammatory conditions (75) including murine models of systemic lupus erythematosus (76), Type I diabetes mellitus (77,78), adjuvant-induced arthritis (79), and experimental cerebral malaria (80). Based on experiments with IFN-γ knock-out mice, one of its primary functions *in vivo* appears to be the activation of macrophages to kill intracellular pathogens such as Mycobacteria (81).

4.1.2.5 IFN-γ-inducing factor:

An IFN-γ-inducing activity was identified in murine Kupffer cells and activated macrophages and referred to as IFN-γ-inducing factor (IGIF) (82). IGIF induces IFN-γ production more potently than does IL-12 and is involved in the development of T_H1 cells. The human homolog has been recently described and shares functions with the murine cytokine such as the induction of IFN-γ production by stimulated PBMC and the enhancement of NK cell cytotoxicity (83). In addition, human IGIF augments GM-CSF production and decreases IL-10 production. It has been proposed that IGIF be designated as Interleukin-18 (IL-18) (83).

5. RECEPTORS OF INFLAMMATORY CYTOKINES

Cytokines elicit their responses by binding to specific high affinity cell-surface receptors on target cells and initiating a series of intracellular signal transduction pathways. The receptors of several cytokines and growth factors are homologous within their extracellular domains. These receptors have been grouped into families, the largest of which is the hematopoietin receptor superfamily which includes one or multiple chains of the receptors for erythropoietin, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-9, IL-11, IL-12, IL-13, IL-15, v-*mpl* oncogene, GM-CSF, G-CSF, prolactin, and growth hormone. The receptors in this family share a common motif of four conserved cysteine residues in the amino-terminal portion of the ligand-binding domain, as well as a conserved stretch of amino acids (WSXWS = Trp-Ser-X-Trp-Ser; X representing a nonconserved residue) proximal to the membrane-spanning region. The receptors also share fibronectin type III domains (84) (Figure 3).

Of the above-mentioned members of the erythropoietin receptor family, one of the best characterized is the IL-2 receptor (IL-2R). It consists of three polypeptide chains: IL-2Rβ (p70) and IL-2Rγ (p64), which are expressed on resting T cells, and IL-2Rα (p55; T cell activation antigen or Tac), which is expressed upon T cell activation. Association of these subunits yields a high affinity receptor for IL-2 (85,86). In addition, Tac (IL-2Rα) is shed from cells in a soluble form, but it has low affinity for IL-2. Soluble IL-2R are elevated in the sera of patients

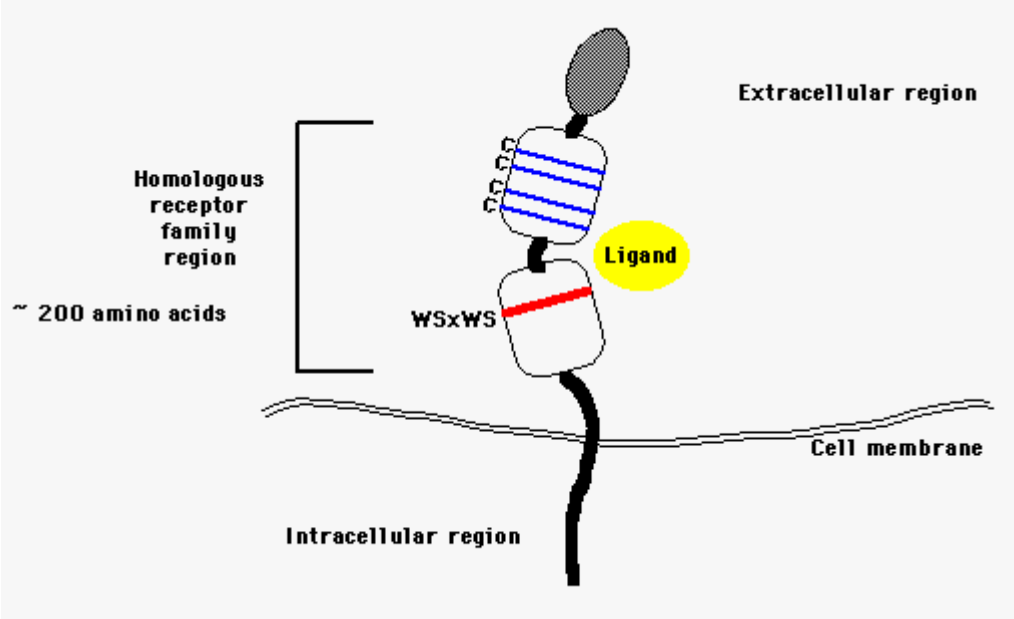

FIGURE 3: Common motifs shared by the erythropoietin receptor family.

with chronic inflammatory disorders such as rheumatoid arthritis and systemic lupus erythematosus (SLE) and the serum levels of soluble IL-2R are reported to correlate with clinical disease activity (87).

Another member of the erythropoietin receptor family, IL-6 receptor (IL-6R), consists of an 80 kDa ligand-binding molecule and a 130 kDa non-ligand binding signal-transducing subunit (gp130). Both molecules exhibit the motifs shared by members of the hematopoietin receptor superfamily (14,88). Such a bimolecular complex is also described for IL-3R, IL-5R, and GM-CSFR. For these receptors, the polypeptide beta c (KH97) is reported to be the accessory molecule (84). One of the biologic consequences of these receptor complexes is that although cytokines bind to specific receptors, some may share common pathways in eliciting the target cell's response as a result of shared receptor components. As an example, IL-6, IL-11, leukemia inhibitory factor (LIF), and oncostatin M recognize different cellular receptors (by virtue of unique ligand-binding subunits), but share the same signal-transducing receptor subunit (gp130) and similar biological activities (Figure 4). These cytokines may therefore exert their effects via common signal transduction pathways (84).

A group of receptors distantly related to the erythropoietin receptor family consists of the receptors for type I (α and β) and type II (γ) interferons (89). Receptors in this class share a homologous binding domain of about 210 amino acids and four cysteine pairs divided equally between the amino and carboxy termini.

Another group of related receptors includes the two receptors for TNF, the receptor for nerve growth factor (NGF), a transmembrane protein, FAS (Apo-1 or CD95), involved in the apoptosis of activated T lymphocytes (90), and CD40, a cell surface receptor important in B cell growth and isotype switching (91). The TNF receptors are 55 kDa (TR55) and 75 kDa (TR75) proteins that bind TNF-α and β equally. Their extracellular domains share 28% identity. There is growing evidence that the two receptors may mediate different cellular responses to TNF (92,93), although there may be crosstalk between the receptors, perhaps at the level of the signalling pathways to which they are coupled.

The chemokine receptors are members of the G protein-coupled receptor (GPCR) superfamily and include IL-8R-A, an IL-8-specific receptor, IL-8R-B, a receptor recognized by IL-8, and other chemokines of the CXC subset. Recently, receptors for the CC subset of chemokines have been identified. They include CC-CKR-1, CC-CKR-2, CC-CKR-3,and CC-CKR-4 and CC-CKR-5 (94). A recently described receptor, the Duffy blood group antigen receptor for chemokines (DARC), binds both CXC and CC chemokines. In addition, the identification of new 'orphan' chemokine receptors, for which no ligands have been identified, has been reported (95). Recently, five groups reported that CC-CKR-5 is a co-receptor for certain strains of HIV-1 (96). A 32-bp deletion in *CKR5* is reported to delay progression to AIDS in infected individuals and may be responsible for the antibody-negative status of individuals exposed to HIV-1 (97).

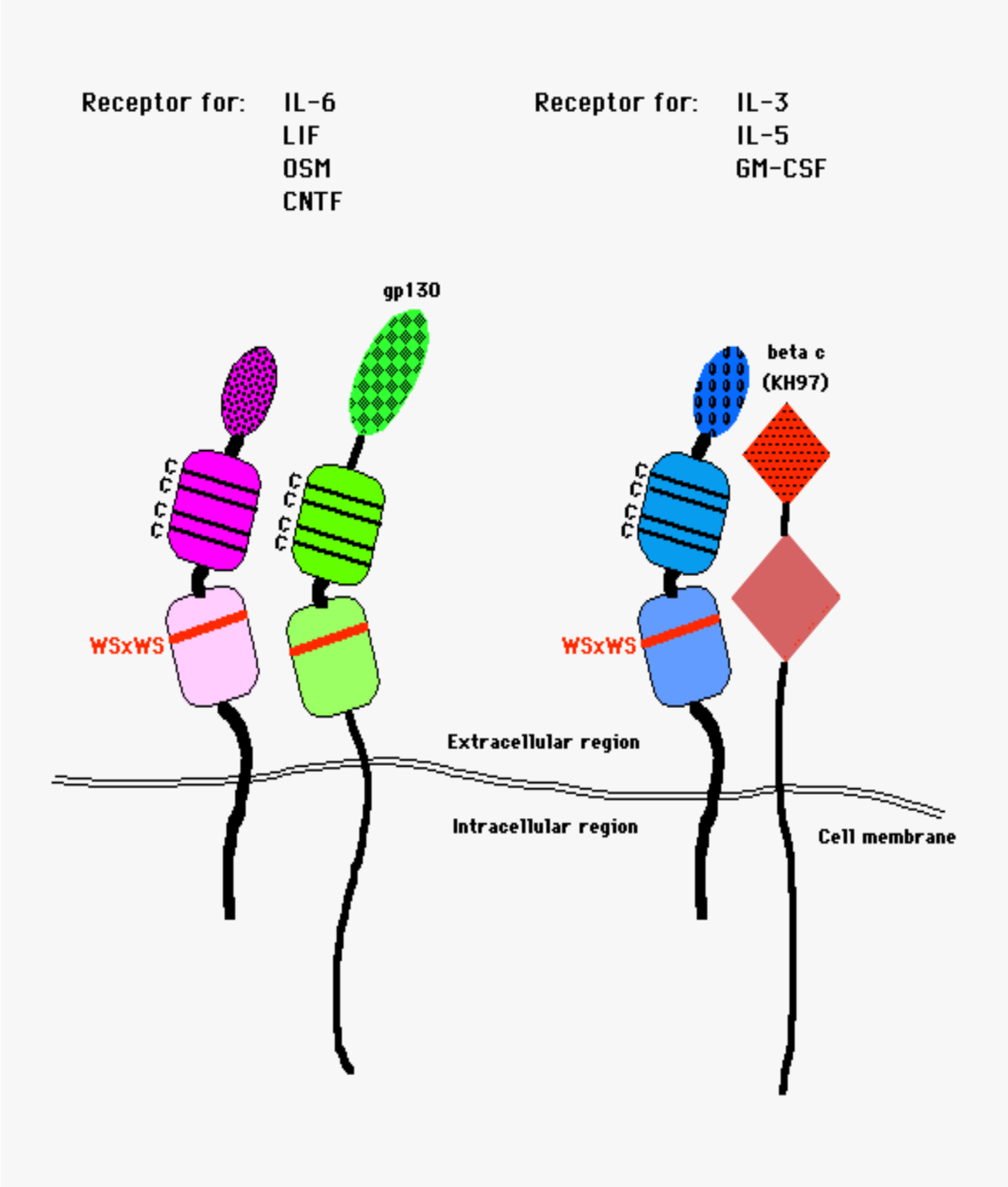

FIGURE 4: Receptors (ligand-binding subunit) and accessory molecules (non-ligand-binding signal-transducing subunit). Abbreviations: IL = Interleukin; LIF = Leukemia inhibitory factor; OSM = Oncostatin M; CNTF = Ciliary neurotrophic factor; GM-CSF = Granulocyte macrophage colony stimulating factor.

6. SUMMARY

In summary, cytokines are key modulators of inflammation. They participate in acute and chronic inflammation in a complex network of interactions. Several cytokines exhibit some redundancy in function and share overlapping properties as well as subunits of their cell surface receptors. Better understanding of the pathways regulated by cytokines will allow the identification and/or development of agents for improved modulation of the inflammatory response for the

treatment of autoimmune, infectious, and neoplastic diseases.

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